

The Unique Biology of Breast Cancer in Young Women

Carey K. Anders, MD

University of North Carolina Chapel Hill

AYA Workshop, NCI June 2009

UNC Case

- 26 year old African American female
 - Self-palpated breast mass at end of pregnancy
 - Mammogram suspicious → Core biopsy
 - Diagnosis = Grade 2, Invasive Breast Cancer
 - ER+/PR+/Her2- and sentinel nodes negative
 - Lumpectomy shows “close” margins → T1cN0
 - Seen for treatment recommendations
 - 4 month old son and 7 yr old daughter at home
 - Supportive mother who lives in PA

Outline

- Epidemiology & Outcomes
- Risk Factors & Clinico-pathologic features
 - Focus on Biology
- Treatment strategies
- Psychosocial Challenges

Estimated New Cases*

US cases, 2007

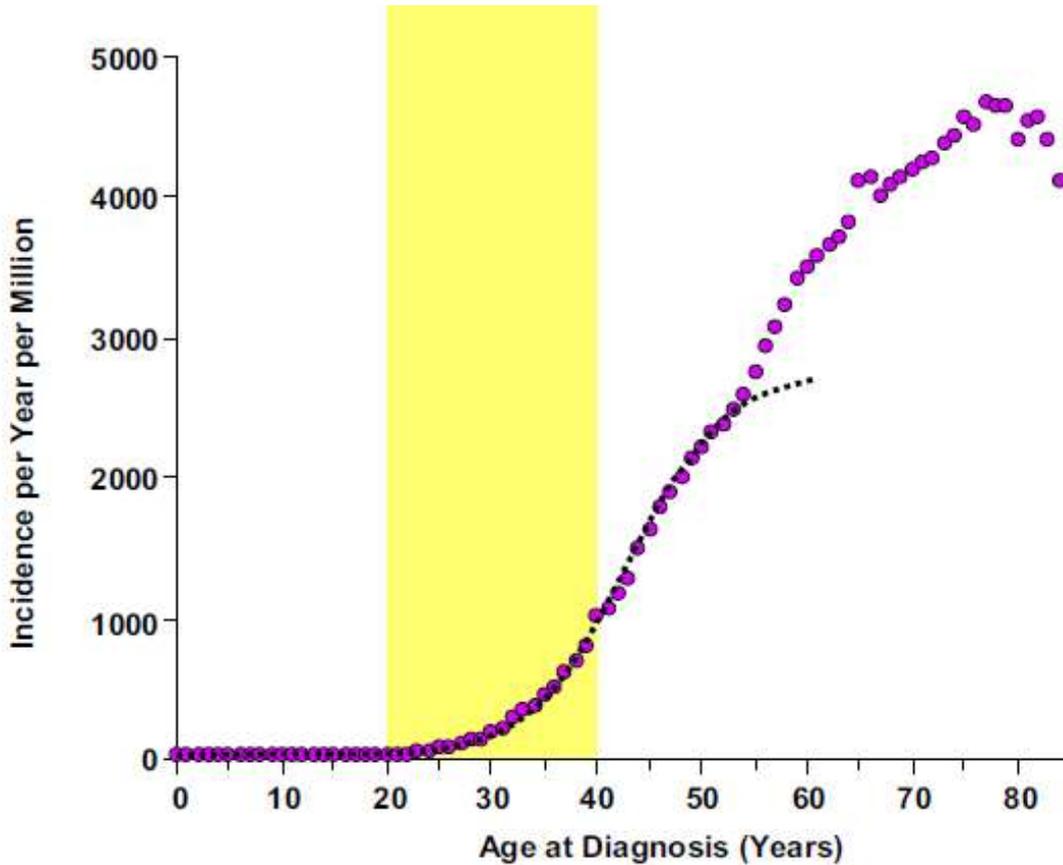
		Males		Females		
Prostate	218,890	29%		Breast	178,480	26%
Lung & bronchus	114,760	15%		Lung & bronchus	98,620	15%
Colon & rectum	79,130	10%		Colon & rectum	74,630	11%
Urinary bladder	50,040	7%		Uterine corpus	39,080	6%
Non-Hodgkin lymphoma	34,200	4%		Non-Hodgkin lymphoma	28,990	4%
Melanoma of the skin	33,910	4%		Melanoma of the skin	26,030	4%
Kidney & renal pelvis	31,590	4%		Thyroid	25,480	4%
Leukemia	24,800	3%		Ovary	22,430	3%
Oral cavity & pharynx	24,180	3%		Kidney & renal pelvis	19,600	3%
Pancreas	18,830	2%		Leukemia	19,440	3%
All Sites	766,860	100%	All Sites	678,060	100%	

Estimated Deaths

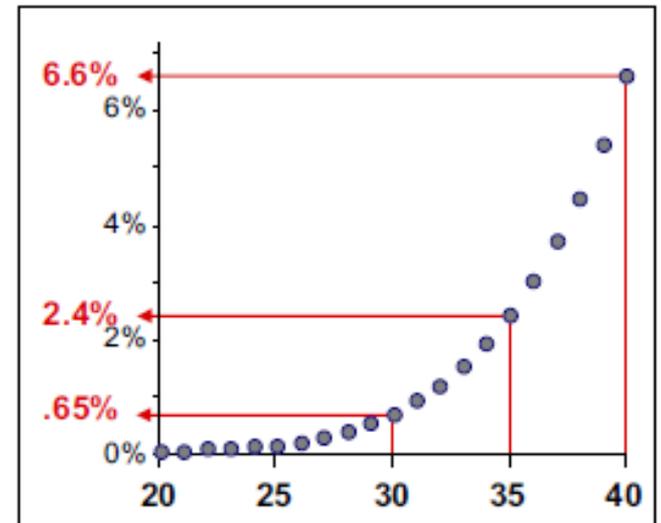
US cases, 2007

		Males		Females		
Lung & bronchus	89,510	31%		Lung & bronchus	70,880	26%
Prostate	27,050	9%		Breast	40,460	15%
Colon & rectum	26,000	9%		Colon & rectum	26,180	10%
Pancreas	16,840	6%		Pancreas	16,530	6%
Leukemia	12,320	4%		Ovary	15,280	6%
Liver & intrahepatic bile duct	11,280	4%		Leukemia	9,470	4%
Esophagus	10,900	4%		Non-Hodgkin lymphoma	9,060	3%
Urinary bladder	9,630	3%		Uterine corpus	7,400	3%
Non-Hodgkin lymphoma	9,600	3%		Brain & other nervous system	5,590	2%
Kidney & renal pelvis	8,080	3%		Liver & intrahepatic bile duct	5,500	2%
All Sites	289,550	100%	All Sites	270,100	100%	

Incidence of breast cancer/yr/million by age



n = 40,000 women
% of all breast cancers by age

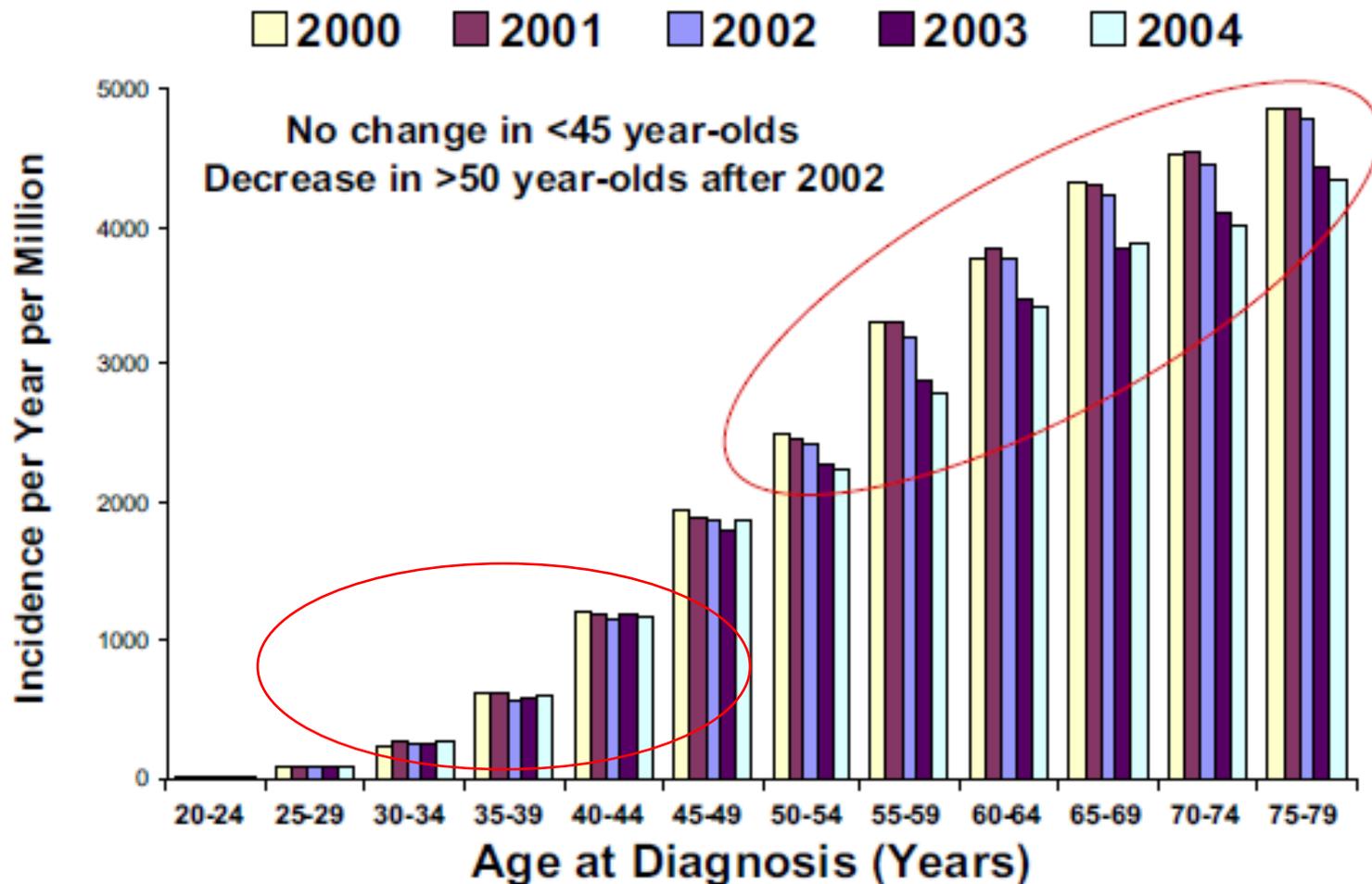


Risk of Breast Cancer by Age

Table 1. Risk of Breast Cancer as Function of Age Estimated From Women Diagnosed in the US SEER17 Registries, 2004

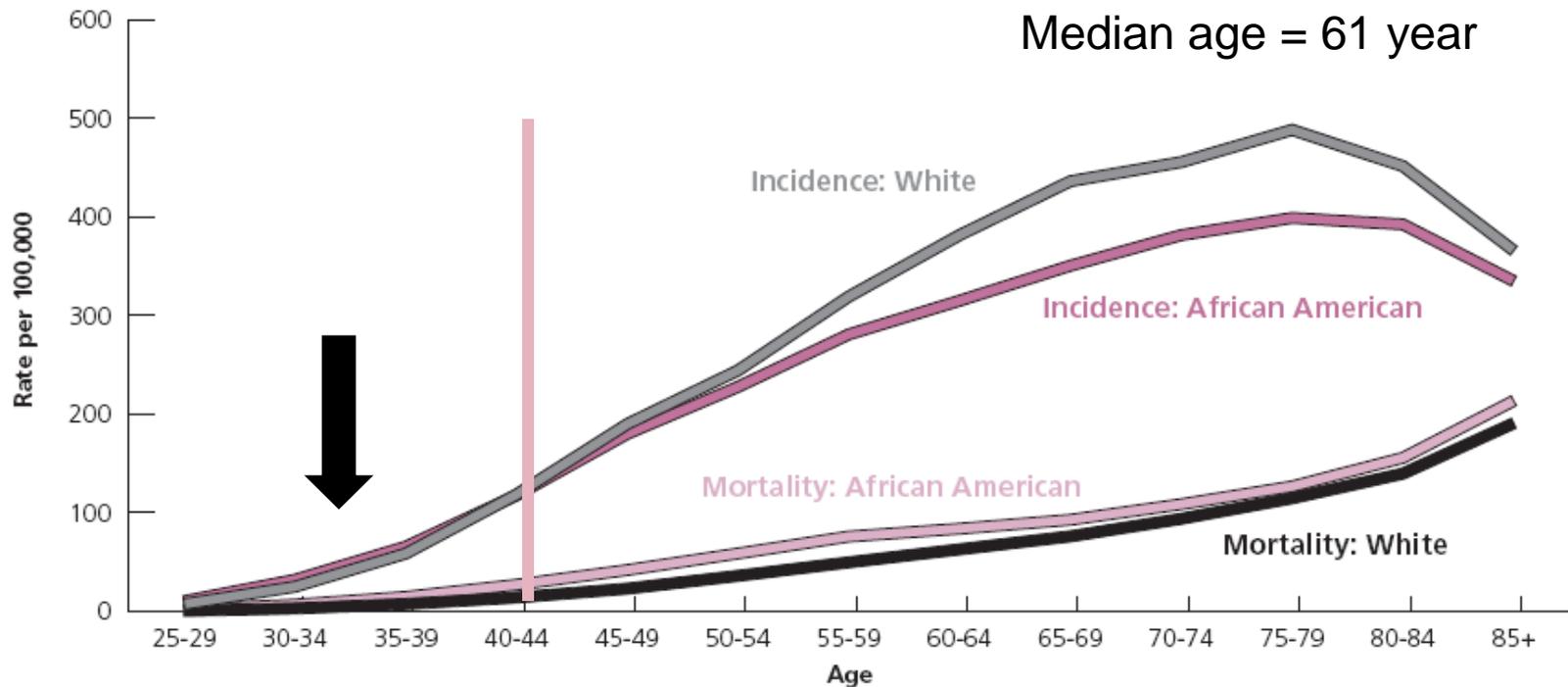
Age (yr)	Risk: 1 in x
15	571,429
20	75,188
25	8,684
30	1,523
35	453
40	173
45	82
50	45
55	30
60	21
65	15
70	12
75	9
80	8
85	7

The incidence of breast cancer is stable in women < 45 years



Breast Cancer Incidence and Mortality by Age and Race

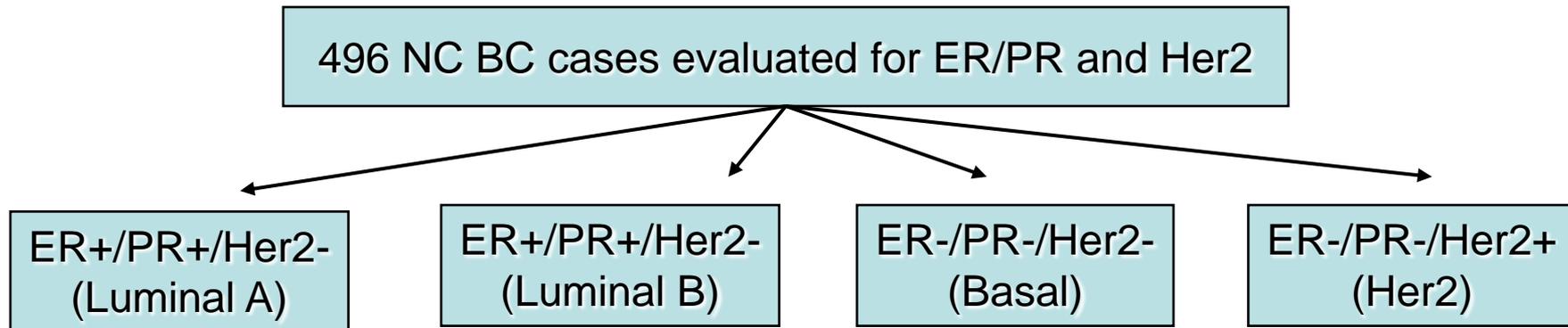
Figure 1. Female Breast Cancer – Incidence and Mortality Rates by Age and Race, US, 2000-2004



Data sources: Incidence – Surveillance, Epidemiology, and End Results (SEER) Program, SEER 17 Registries, 2000-2004, Division of Cancer Control and Population Science, National Cancer Institute, 2007. Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, 2007. American Cancer Society, Surveillance Research, 2007

Adapted from the ACS, Breast Cancer Facts and Figures 2007-8

Race, Breast Cancer Subtypes, and Survival in the Carolina Breast Cancer Study



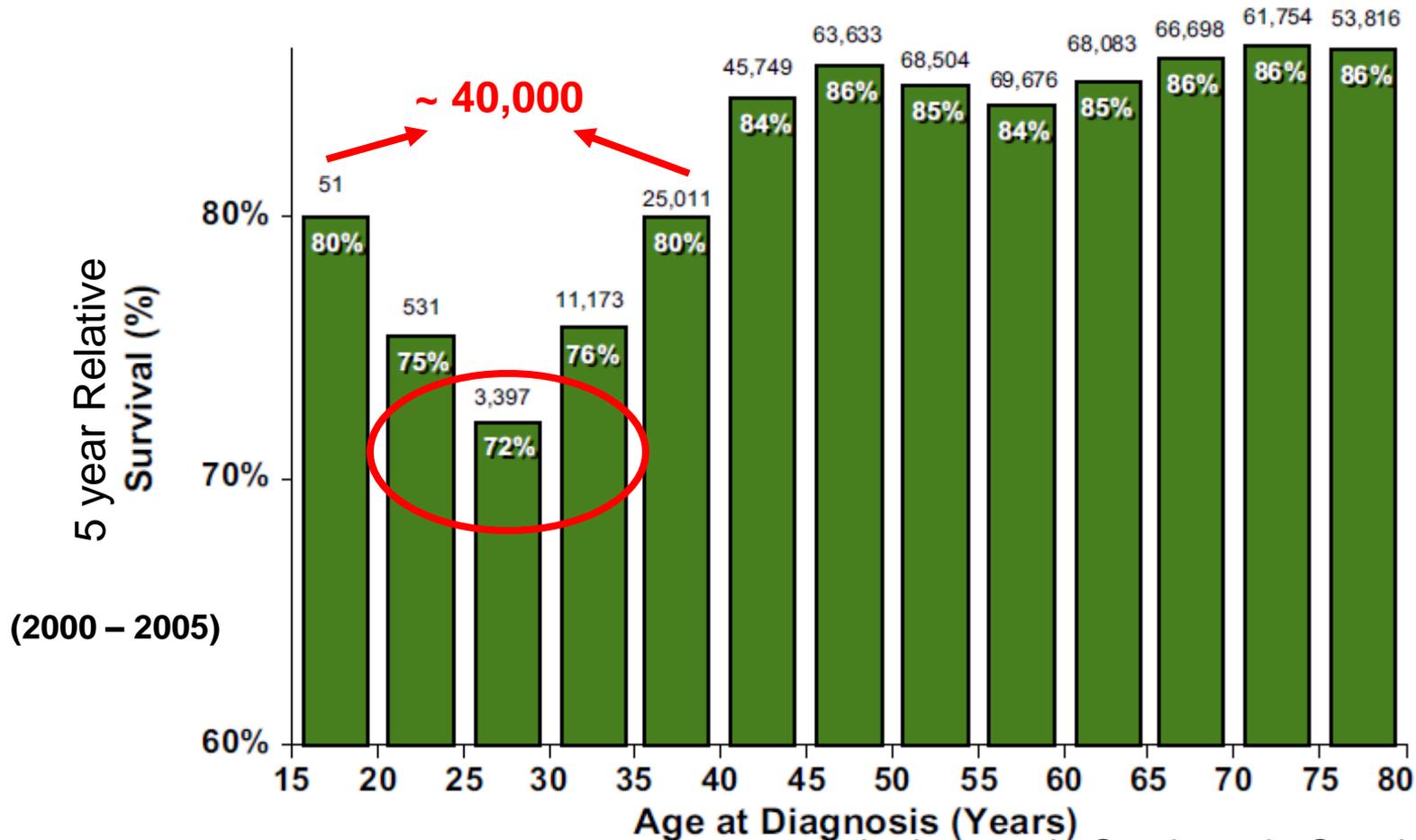
Goal: To identify of breast cancer subtype in racial and menopausal subgroups

Table 1. Characteristics of Carolina Breast Cancer Study Patients With Immunohistochemical Marker Data

Characteristic	No. (%)						P Value*
	All Cases (N = 496)	Basal-like (n = 100)	HER2+/ER- (n = 33)	Luminal A (n = 255)	Luminal B (n = 77)	Unclassified (n = 31)	
Age, mean (SD), y	50 (12)	46 (10)	47 (9)	52 (12)	50 (12)	45 (11)	<.001
Race							
African American	196 (40)	52 (52)	16 (48)	93 (36)	25 (32)	10 (32)	.03
Non-African American	300 (60)	48 (48)	17 (52)	162 (64)	52 (68)	21 (68)	
Menopausal status							
Premenopausal	261 (53)	64 (64)	18 (55)	118 (46)	39 (51)	22 (71)	.008
Postmenopausal	235 (47)	36 (36)	15 (45)	137 (54)	38 (49)	9 (29)	

Breast Cancer Outcomes

- Breast cancer survival is lower for women < 40 years of age across all subtypes and stages.



Risk Factors

Clinico-pathologic Features

Risk Factors associated with premenopausal breast cancer

- Obesity
- High caloric intake
- Sedentary lifestyle
- Mantle radiation (i.e. Hodgkin's)
- Early age at menarche
- Heavy alcohol intake
- High intake of red meat
- High breast density



Digital Mammography

Silvera et al. Br Cancer Res Treat 2006.

Cho et al. Arch Intern Med 2006.

McCormick et al. Cancer Epid Biomarkers Prev 2006.

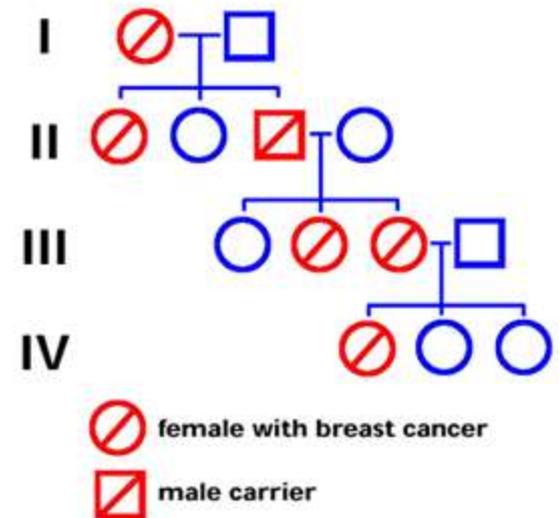
Do et al. Int J Vitamin Nutr Res 2007.

Slattery et al. Ann Epid 2007.

Familial Risks and Breast Cancer

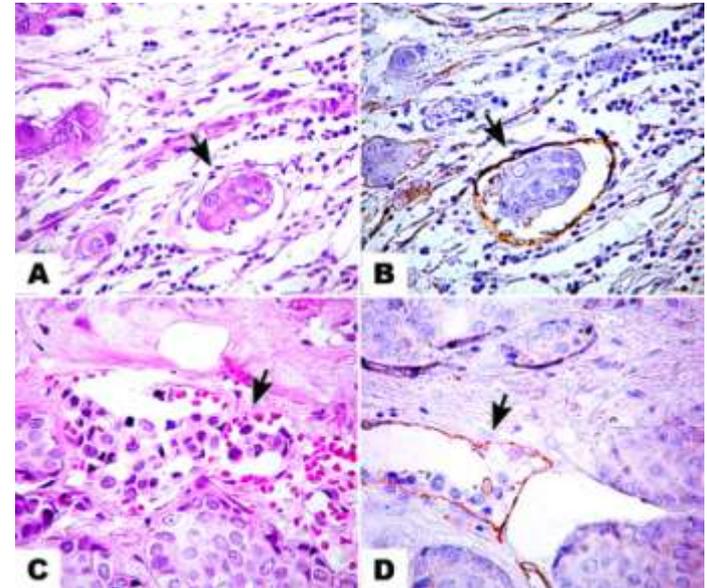
- Early onset breast cancer is associated with a positive family history
- < 30 years of age and BC + family history = 50% risk of germline mutation (**BRCA1, BRCA2, PTEN or TP53**)
- < 10% risk of germline mutation if family history negative

Pedigree of a Family with Hereditary Breast Cancer



Aggressive Clinico-Pathologic Features of Breast Cancer in Young Women

- Women < 35 yrs of age, have higher % of ER and PR negative breast tumors and LVI ($p < 0.001$) compared to those aged 35 – 50 years
- Differences in T size, nodal and Her2 status have been less clear across studies



Adapted from Marinho *et al.* *BMC Cancer* 2008 **8**:64

Adami *et al.* *NEJM* 1986.
El Saghir *et al.* *BMC* 2006.
Holli *et al.* *Eur J Cancer* 1997.

Colleoni *et al.* *Ann Oncol* 2002.
Anders *et al.* *JCO* 2008.
Albain *et al.* *JNCI* 1994.

Young Age Alone Adversely Affects Prognosis

- Despite discrepancies in adverse prognostic features, younger age in several studies in an **INDEPENDENT** predictor of adverse outcome

Nixon et al. JCO 1994

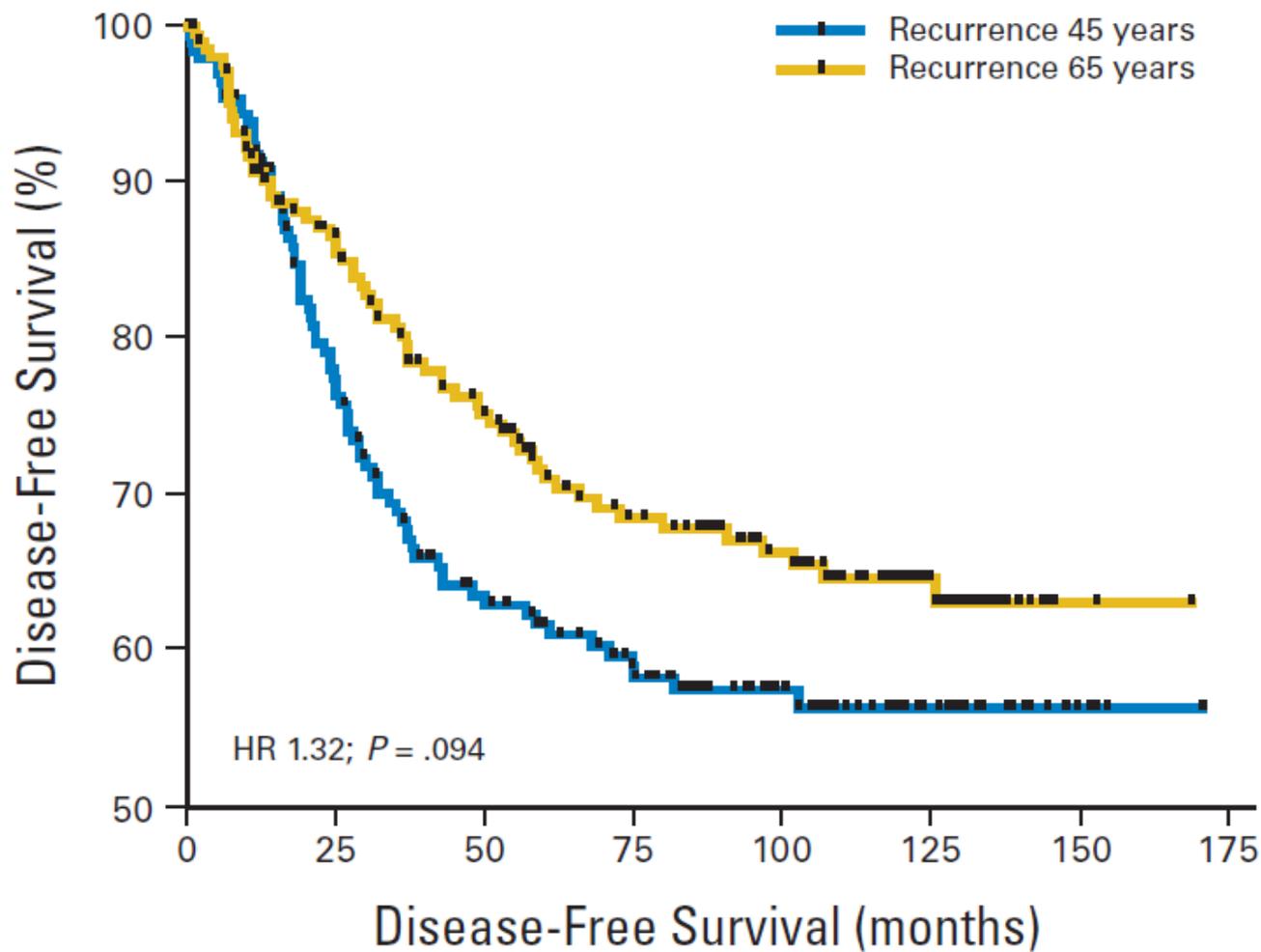
> 1,200 women with early stage breast cancer

MV analysis indicates AGE < 35 a powerful **INDEPENDENT** prognostic factor

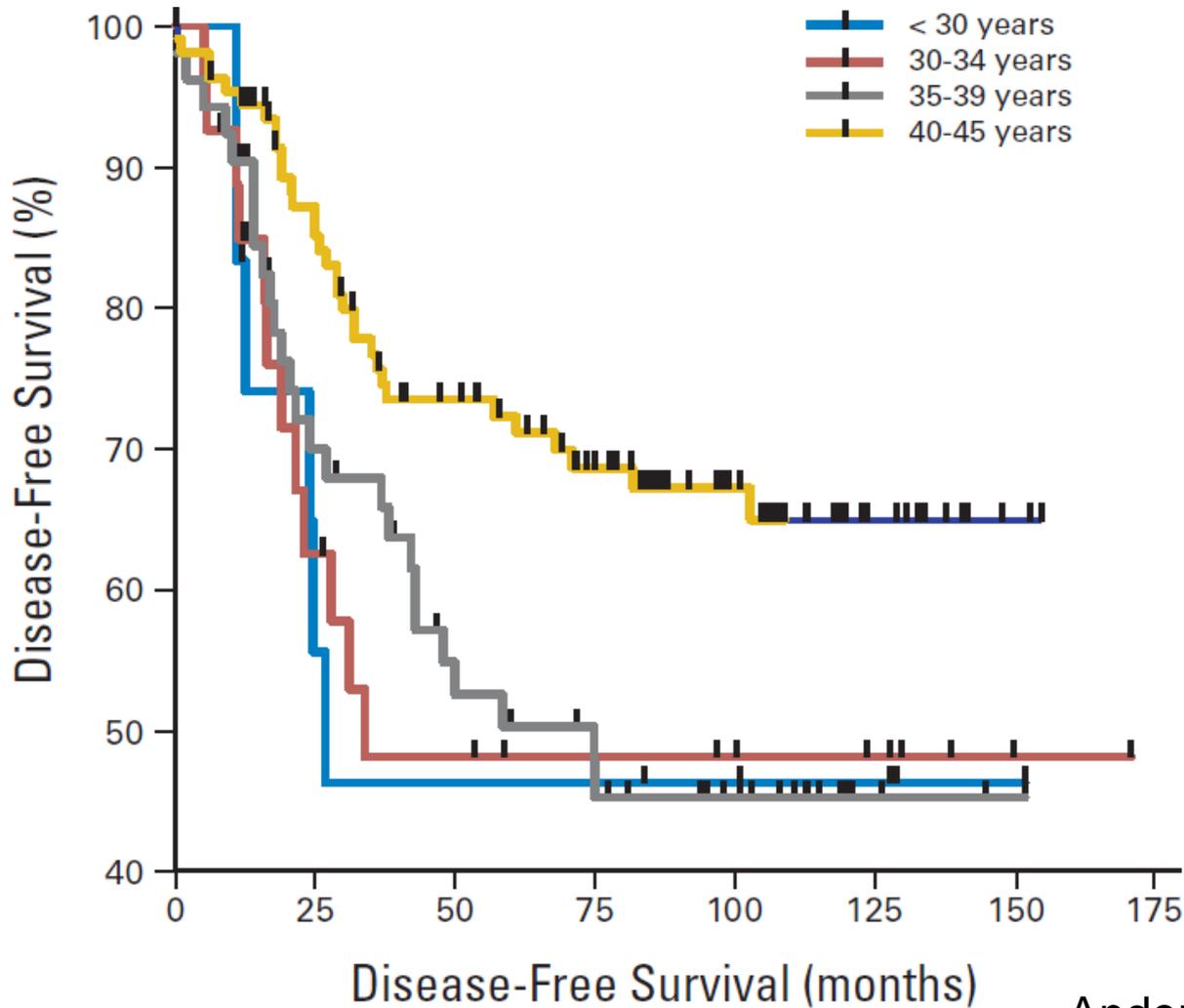
- Time to recurrence RR = 1.7 (p < 0.001)
- Time to distant failure RR = 1.6 (p < 0.009)
- Overall mortality RR = 1.5 (p < 0.004)

Indicates adverse prognosis is not solely a result of adverse features
....points toward a unique biology.

Inferior Prognosis among Younger Women (≤ 45 years)



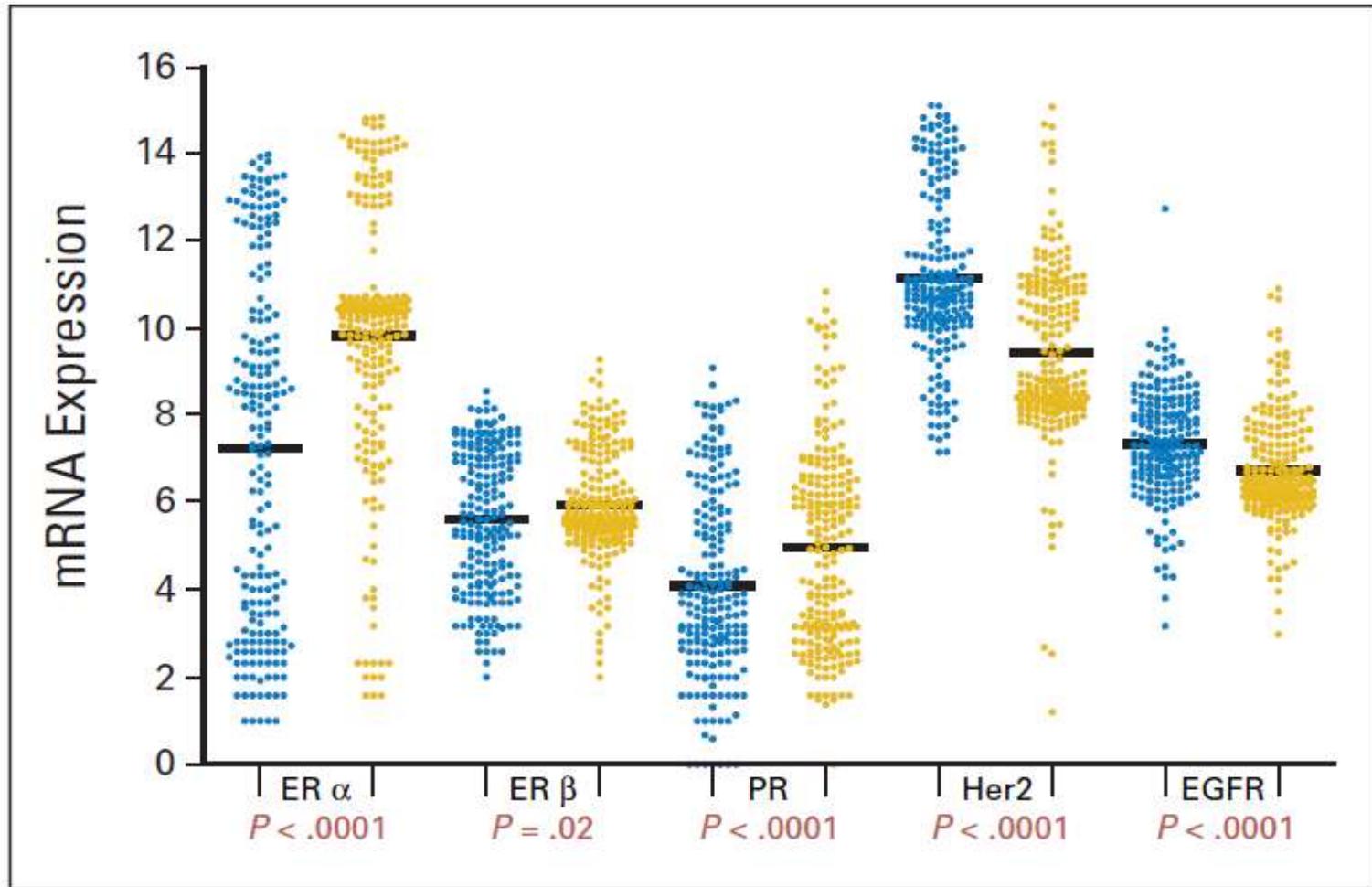
Inferior Prognosis among the *Youngest* women (< 40 years)



Age-specific differences in clinico-pathologic features plus mRNA Expression

Clinical Status	Women Age ≤ 45 Years	Women Age ≥ 65 Years	<i>P</i>
Positive ER status, %*	71	80	.027
ER α mRNA expression	7.2	9.8	< .0001
ER β mRNA expression	5.6	5.9	.02
Positive PR status, %*	75	50	.32
PR mRNA expression	4.1	5.0	< .0001
HER-2, 2-3+, %†	52	24	.075
HER-2 mRNA expression	11.1	9.4	< .0001
EGFR mRNA expression	7.3	6.7	< .0001
Tumor grade 3, %	56	26	< .0001
Tumor size > 2 cm, %	62	47	.012
Lymph node positive, %	38	25	.008

Age-specific differences in mRNA expression



Blue < 45 yrs; Red > 65 yrs

Anders et al. JCO 2008.

Uni- & Multivariate Analysis: Women \leq 45 years

Table 3. Univariate and Multivariate Analysis of Clinicopathologic Variables and Gene Expression Profiles

Variable	Hazard Ratio	Worse Prognosis	<i>P</i>
Women age \leq 45 years			
Univariate analysis			
Age	2.13	Younger	< .001
Tumor size	1.97	> 2 cm	.032
Lymph node	1.60	Positive	.043
ER β *	1.18	Lower	.024
Multivariate analysis			
Age	1.96	Younger	.004
ER β *	1.41	Lower	.012
EGFR*	1.24	Higher	.026
ER α *	1.08	Higher	.16
Tumor size	1.41	> 2 cm	.16

*mRNA expression values

Anders et al. JCO 2008.

Uni- & Multivariate Analysis: Women \leq 65 years

Table 3. Univariate and Multivariate Analysis of Clinicopathologic Variables and Gene Expression Profiles

Variable	Hazard Ratio	Worse Prognosis	<i>P</i>
Women age \geq 65 years			
Univariate analysis			
Nuclear grade	3.56	3	< .001
Tumor size	2.81	> 2 cm	< .001
Lymph node	2.41	Positive	< .001
ER β *	1.25	Lower	.048
Multivariate analysis			
ER β *	1.40	Lower	.034
Lymph node	1.88	Positive	.04
Nuclear grade	1.85	3	.069
ErbB2*	1.11	Higher	.12
ER status†	1.69	Negative	.13
ER α *	1.11	Higher	.14
Tumor size	1.46	> 2 cm	.16

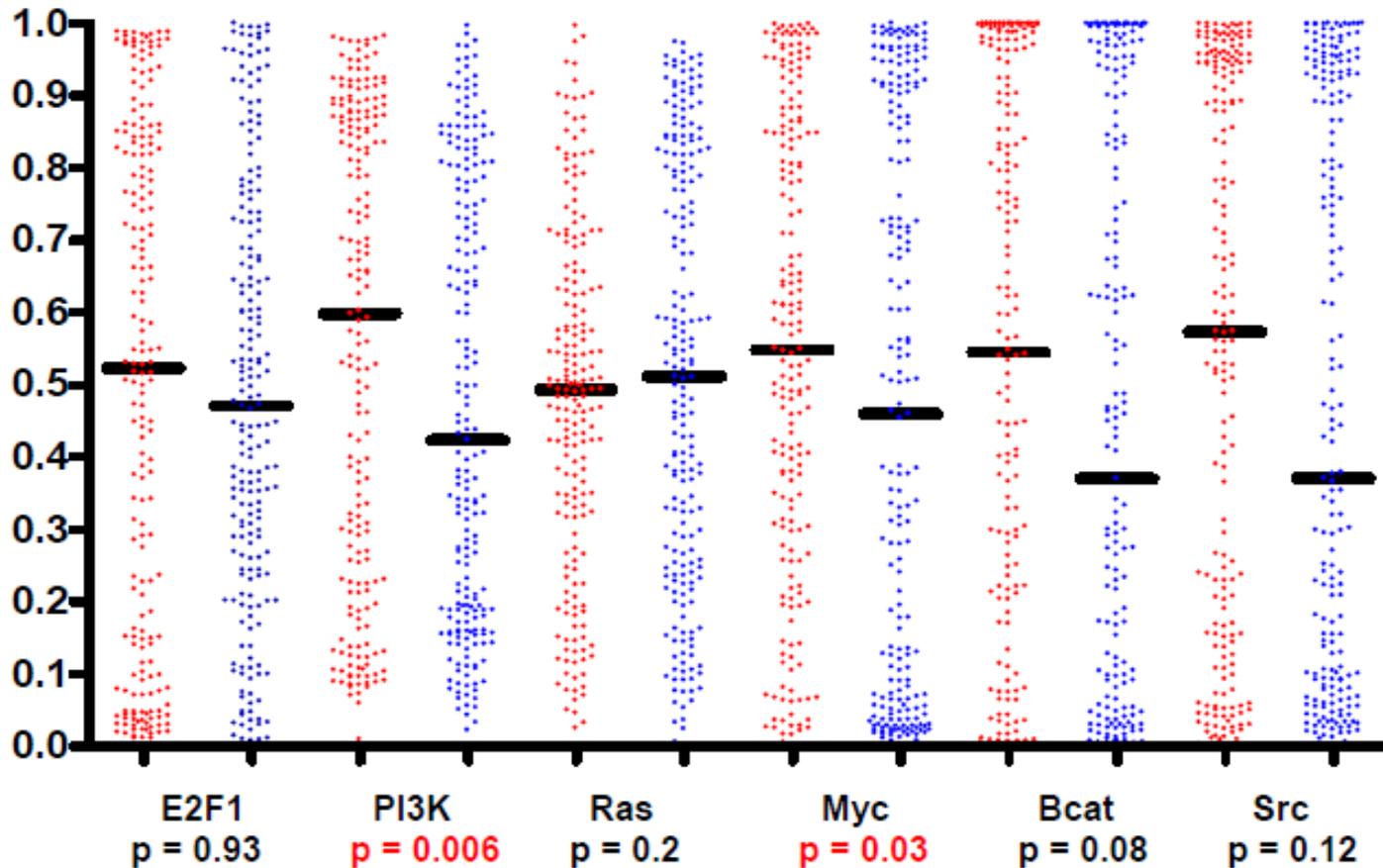
*mRNA expression values

Anders et al. JCO 2008.

Single Gene and Gene Set Results

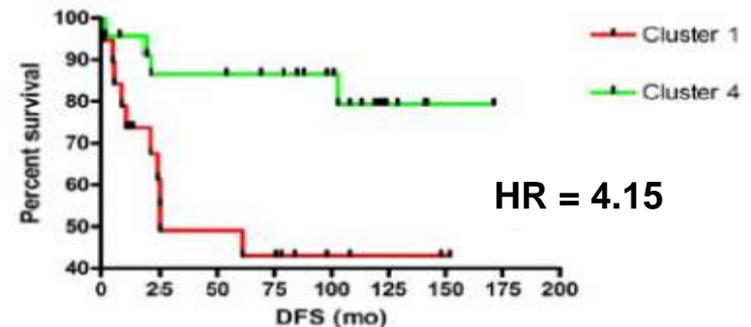
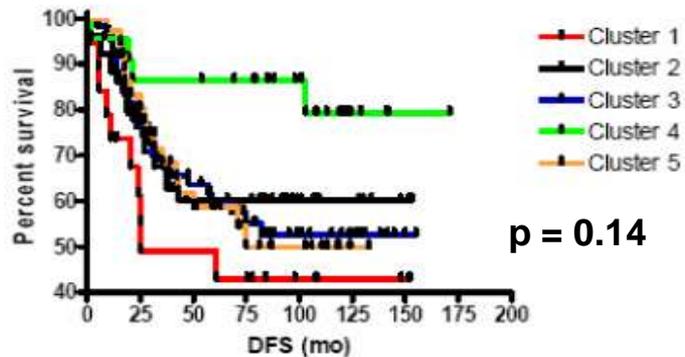
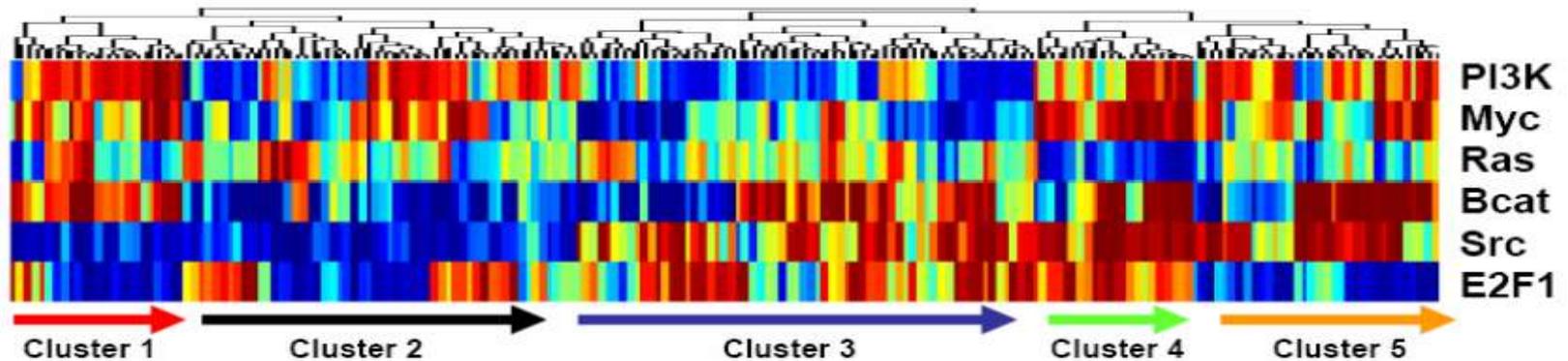
- **Single Gene Analysis**
 - No statistically significant difference in top 50 genes differentially expressed between young and old
- **Gene Set Enrichment Analysis (GSEA)**
 - 367 gene sets preferentially expressed in young women's tumors
 - mTOR pathway, hypoxia, BRCA1, stem cell, apoptosis, HDAC
 - Multiple oncogenic signaling pathways including: Myc, E2F, Ras, β -catenin, AKT, p53, PTEN, and MapKinase pathways
 - No common gene sets identified among older women's tumors

Age-specific differences in oncogenic signaling pathways



Oncogenic Pathway Patterns: Young Women

Age ≤ 45 years; n=200



Oncogenic Pathway Patterns: Older Women

Age ≥ 65 years; n=211

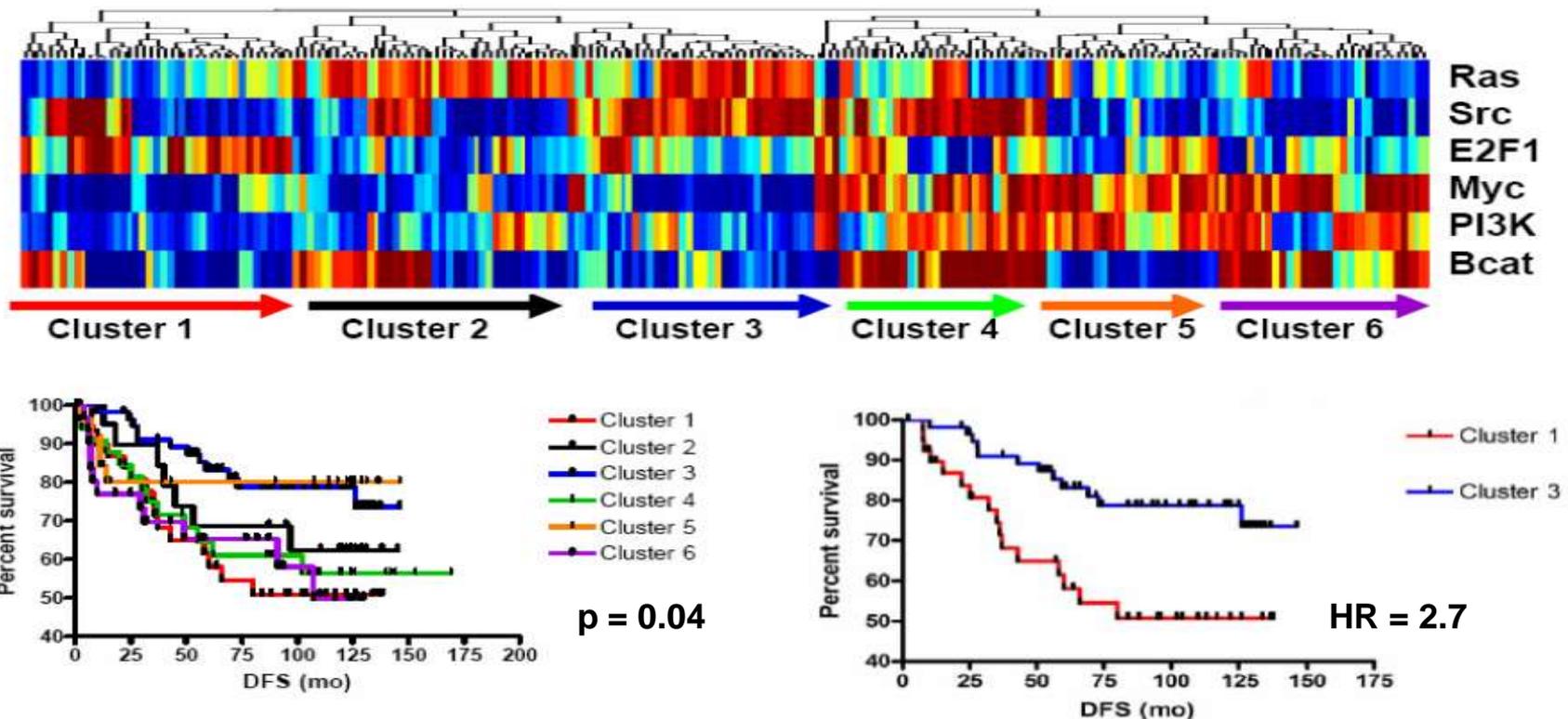


Bild et al. Nature 2006.
Anders et al. PLoS ONE 2008.

Treatments: Local Therapies

The basic approach for adolescents and young adults is similar to older women

Surgical Management:

Two Principles to consider when deciding between BCT and Mastectomy →

- 1) Local Recurrence risk
- 2) Overall cosmetic result

Table 1. Crude Rate of Recurrence in the Treated Breast for 1,683 Stage I-II Patients Treated With Conservative Surgery and Irradiation Between November 1963 and December 1982 as a Function of Age

Age (yrs)	Local Failure (%)	<i>P</i>
34 or less	20/109 (18.4)	
35-39	32/134 (23.9)	
Total	52/243 (21.4)	
40-44	29/249 (11.7)	
45-49	28/319 (8.8)	
50-54	30/254 (11.8)	
55-59	14/204 (6.9)	
60-64	13/160 (8.1)	
65-69	14/133 (10.5)	
70 or more	5/121 (4.1)	
Total	133/1,440 (9.2)	<i>P</i> < .001

F/up study illustrated higher prevalence of aggressive morphologic features (i.e. higher grade, DCIS, unfavorable margins) among women aged less than 40

NOTE. Median follow-up, 11 years.

Kurtz et al. Int J Rad Onc Biol Phys 1988.
Kurtz et al. JCO 1990.

Treatments: Systemic Therapies

The basic approach for adolescents and young adults is similar to older women

Chemotherapeutics:

Main Principles to consider when deciding on regimen→

- 1) Extent of disease (TNM staging)
- 2) Side effects→
 - a) Immediate -- usually fewer comorbidities
 - b) Long-term -- survivorship (ie. fertility, premature menopause)

Standard Therapies

Adjuvant

Anthracycline/Taxanes in the Node+
Tamoxifen in ER+/PR+
Trastuzumab in Her2+

&

Metastatic

Single agent chemotherapeutics
Bevacizumab in Her2-
Trastuzumab in Her2+

Investigational Strategies

Adjuvant

Ovarian Suppression in ER+/PR+
OS + AI in ER+/PR+
Bisphosphonates

&

Metastatic

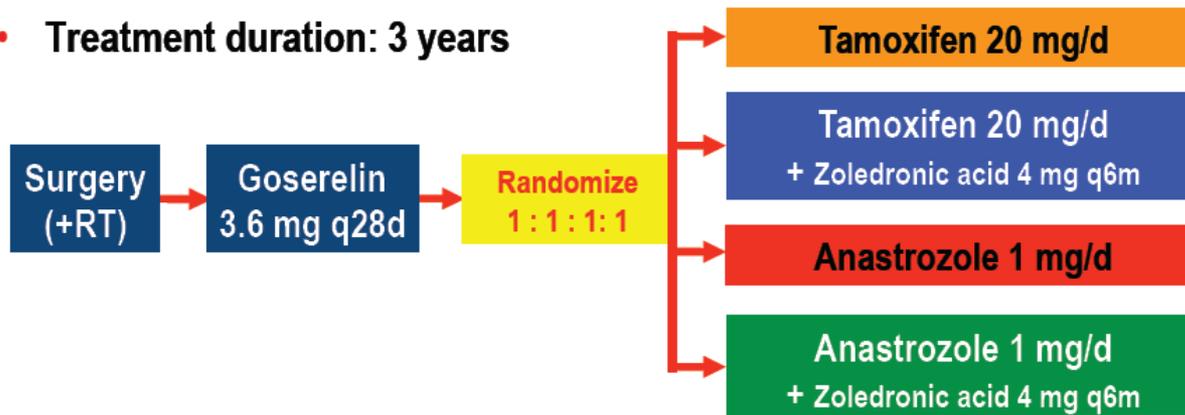
PARP inhibitors in BRCA-associated BC
T-DM1 in Her2+

Endocrine Therapy in Premenopausal Women: Beyond Tamoxifen

- **ABCSG 12** sought to answer 2 ?s:
 - Can AI's improve outcome compared with tamoxifen?
 - Can bisphosphonates add to endocrine therapy?

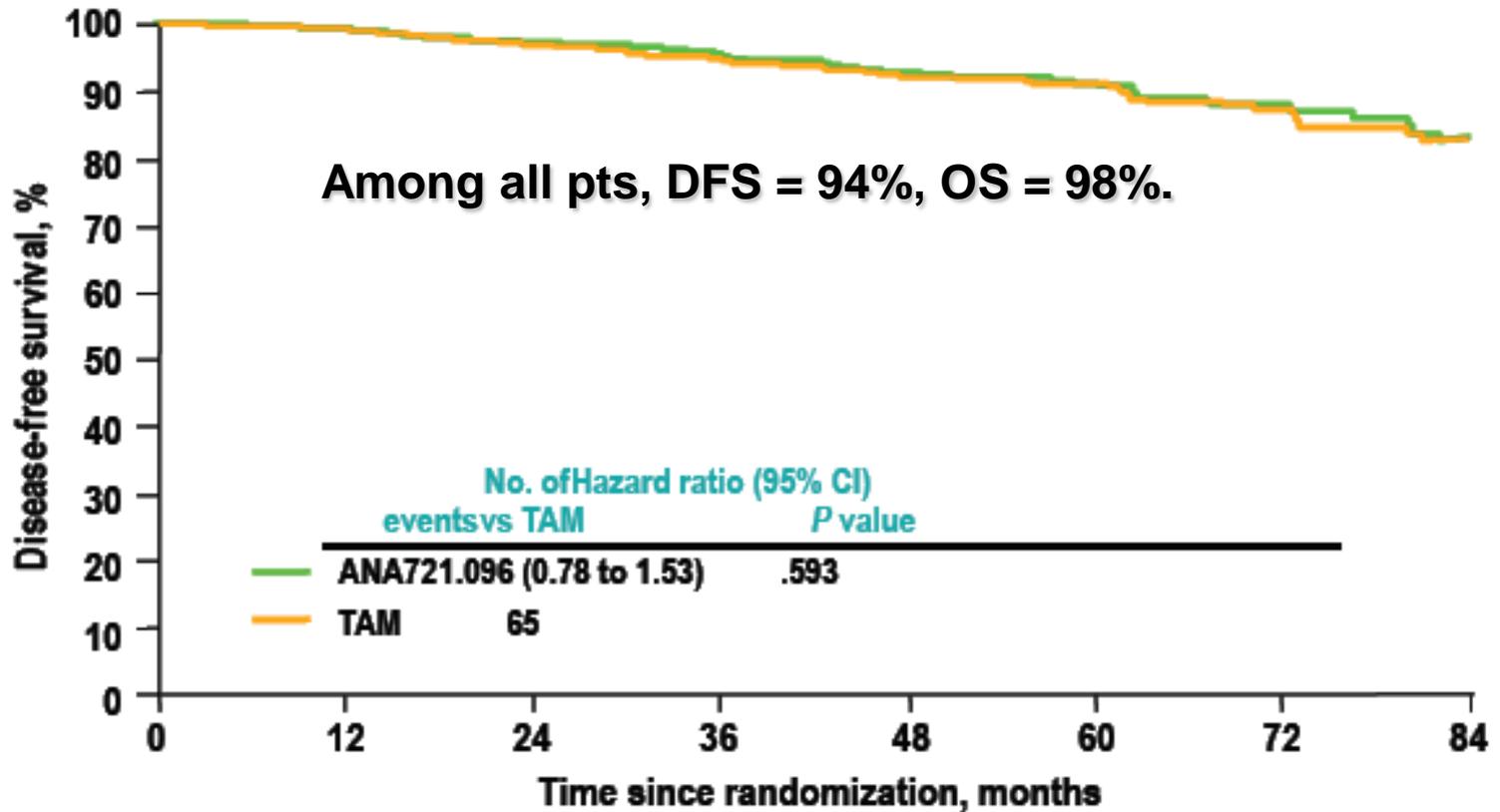
ABCSG-12 Trial Design

- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



Primary Endpoint: Disease-Free Survival

No Significant Difference Between TAM and ANA



Number at risk

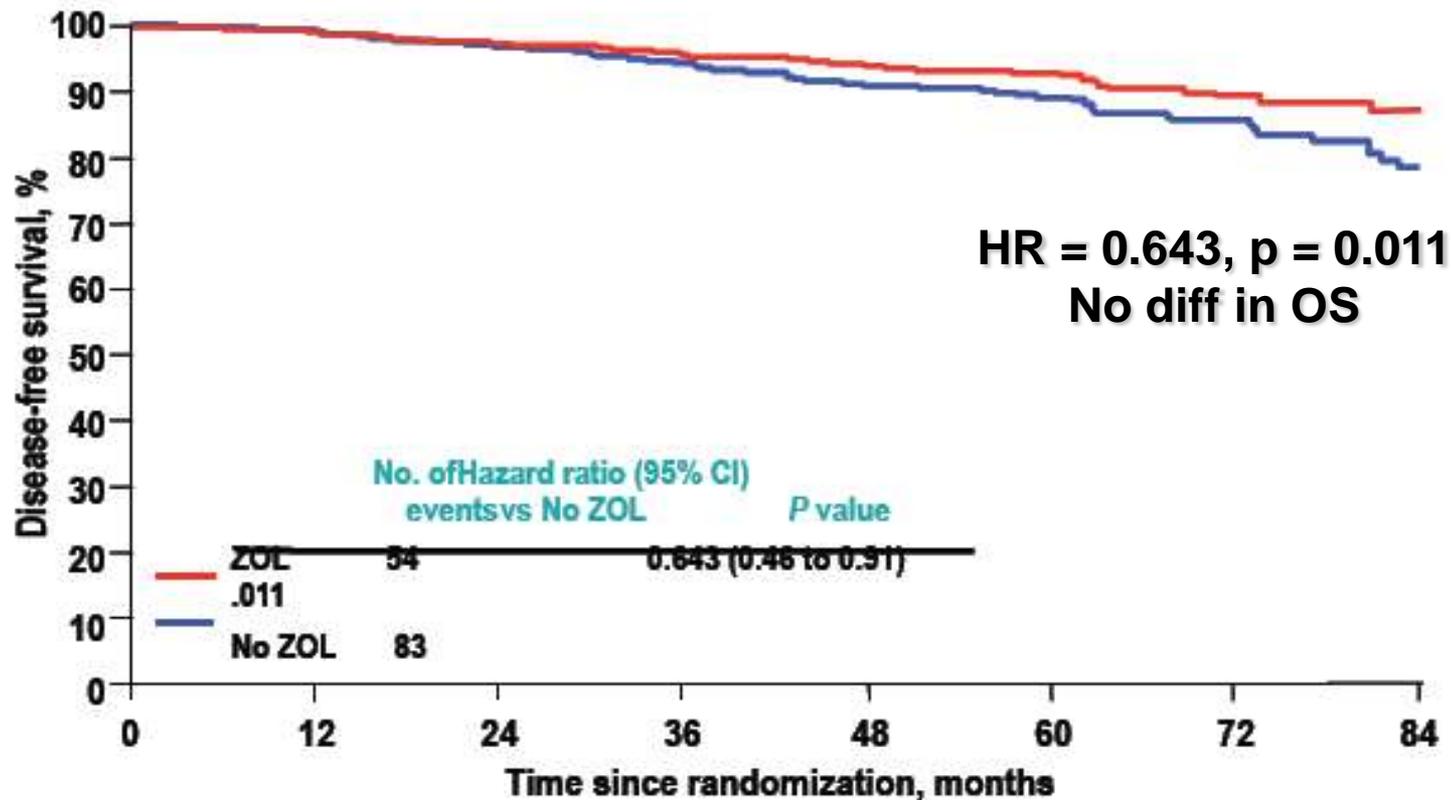
TAM	900	840	736	580	439	264	141	60
ANA	903	849	743	558	436	271	151	59

ASCO 2008 Annual Meeting, Chicago, June 1st

Gnant et al. ASCO 2008.

Primary Endpoint: Disease-Free Survival

Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



Number at risk

No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

Quality of Life/Psychosocial Issues

Sexuality and Body Image

Depression/Anxiety

Hot flashes

**Breast Cancer Diagnosis
at a Young Age**

Loss of Control

Loss of Fertility

Emotional and social functioning

Premature menopause

Interactions with spouse/children

Per ClinicalTrials.gov, “Quality of Life in Female Breast Cancer Survivors and Their Spouse, Partner, or Acquaintance” through ECOG/NCI, PI: Victoria Champion, #NCT00309933. (2 cohorts, 18 – 45 and 55 – 78)

Back to our case...

- Patient in midst of adjuvant therapy
 - Completed 3 of 4 cycles of dose dense AC
 - Surgical recommendations are for completion mastectomy +/- immediate reconstruction
 - BRCA1/2 status is pending
 - Will dictate prophylactic surgical decisions
 - Plan for 5 years of Tamoxifen
 - Will offer S0307 adjuvant bisphosphonate trial
 - Patient and family are adjusting well

Conclusions

- Although risk increases with age, breast cancer affects ~40,000 women aged < 40 years
- Breast cancer at a young age is associated with unique risk factors, adverse clinico-pathologic features, and poorer prognosis – INDEPENDENT of age
- Genomic studies illustrate a rich biology among breast cancers arising in a younger host; may offer novel therapeutic opportunities
- Treatment strategies (both local and systemic) must be individualized
- Psychosocial factors must be considered when treating younger women facing breast cancer

UNC Lineberger Cancer Center



UNC Cancer Hospital

UNC Lineberger Cancer Center



Breast Cancer Clinical Staff

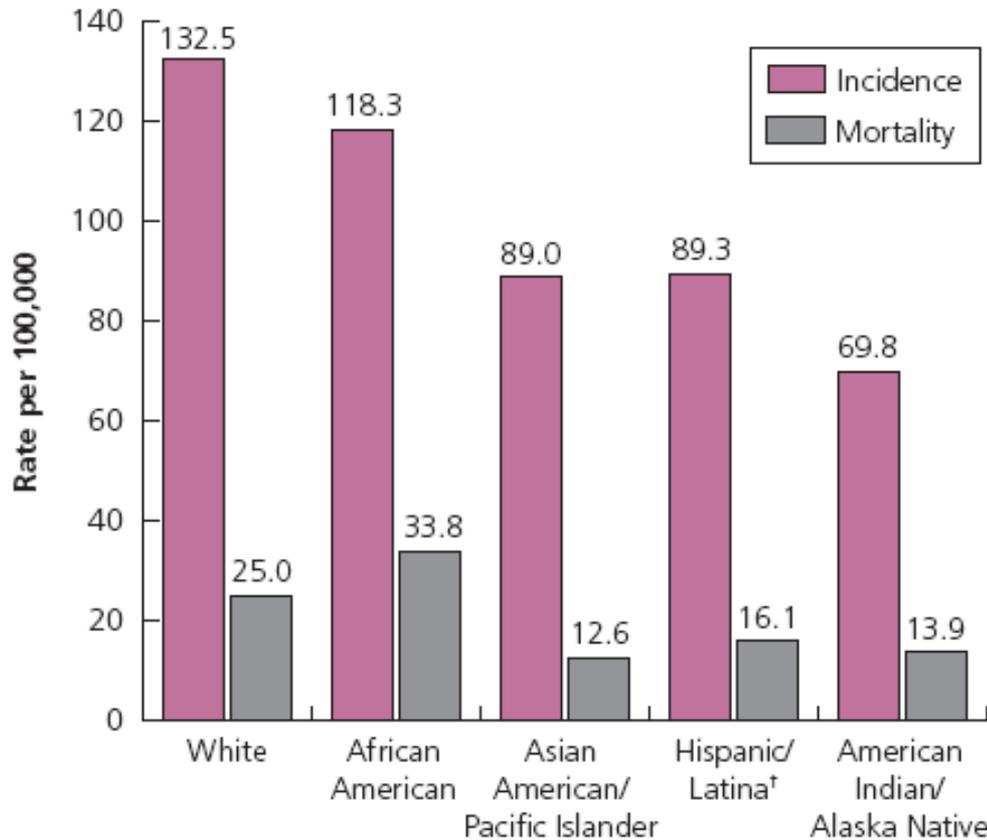
Thank you

Questions?

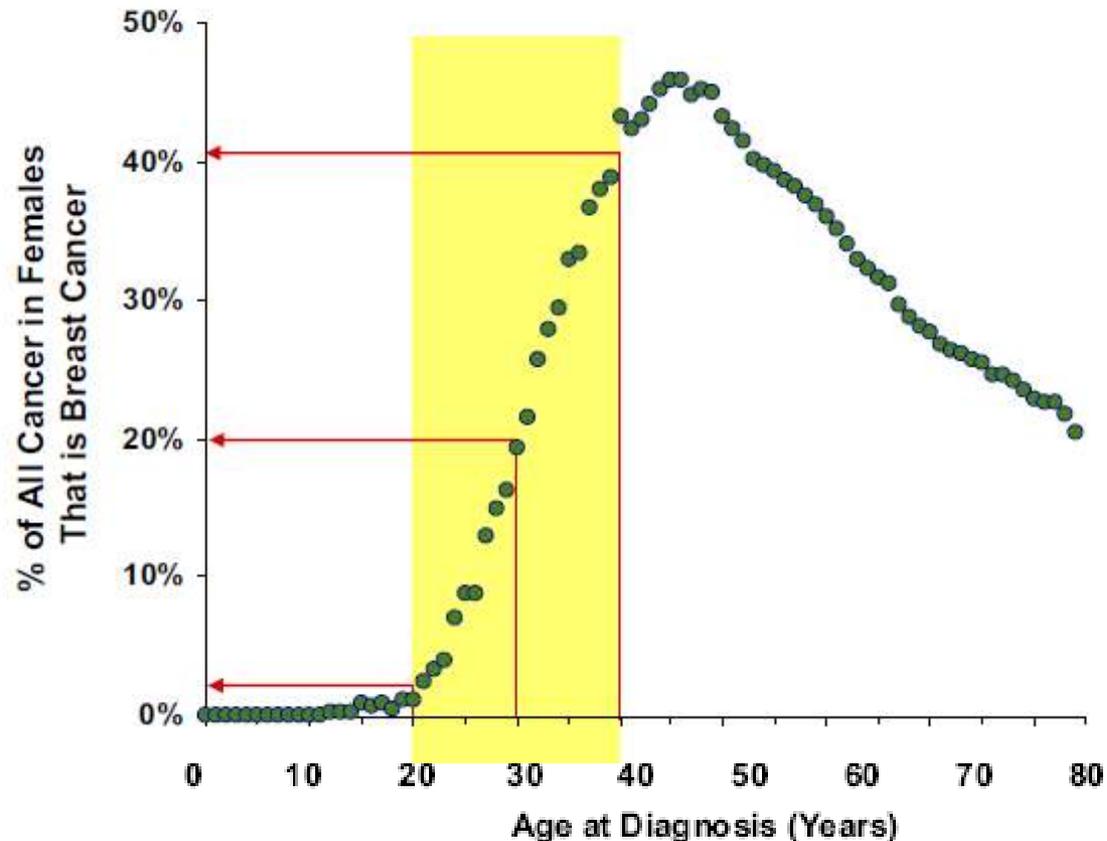
Extra slides

Incidence and Mortality by Race/Ethnicity

Figure 2. Female Breast Cancer Incidence and Mortality Rates* by Race and Ethnicity, US, 2000-2004

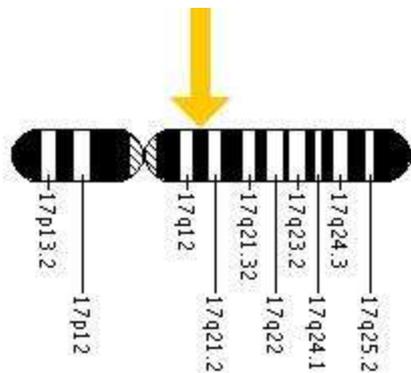


Breast Cancer Incidence (among all cancers) in Females by Age

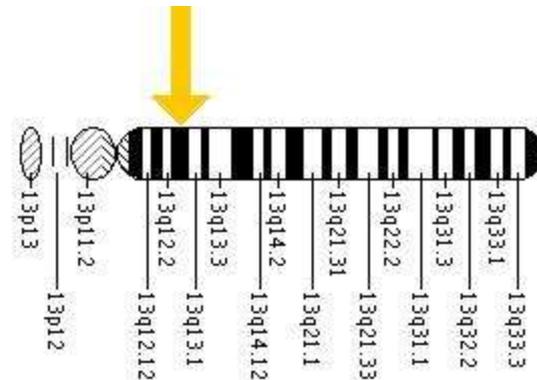


Familial Risks and Breast Cancer

- Early onset breast cancer is associated with with positive family history
 - < 30 years of age and BC + family history = 50% risk of germline mutation (**BRCA1, BRCA2, PTEN or TP53**)
 - < 10% risk of germline mutation if family history negative



BRCA1, Chromosome 17



BRCA2, Chromosome 13